Understanding cognitive decline in Multiple Sclerosis

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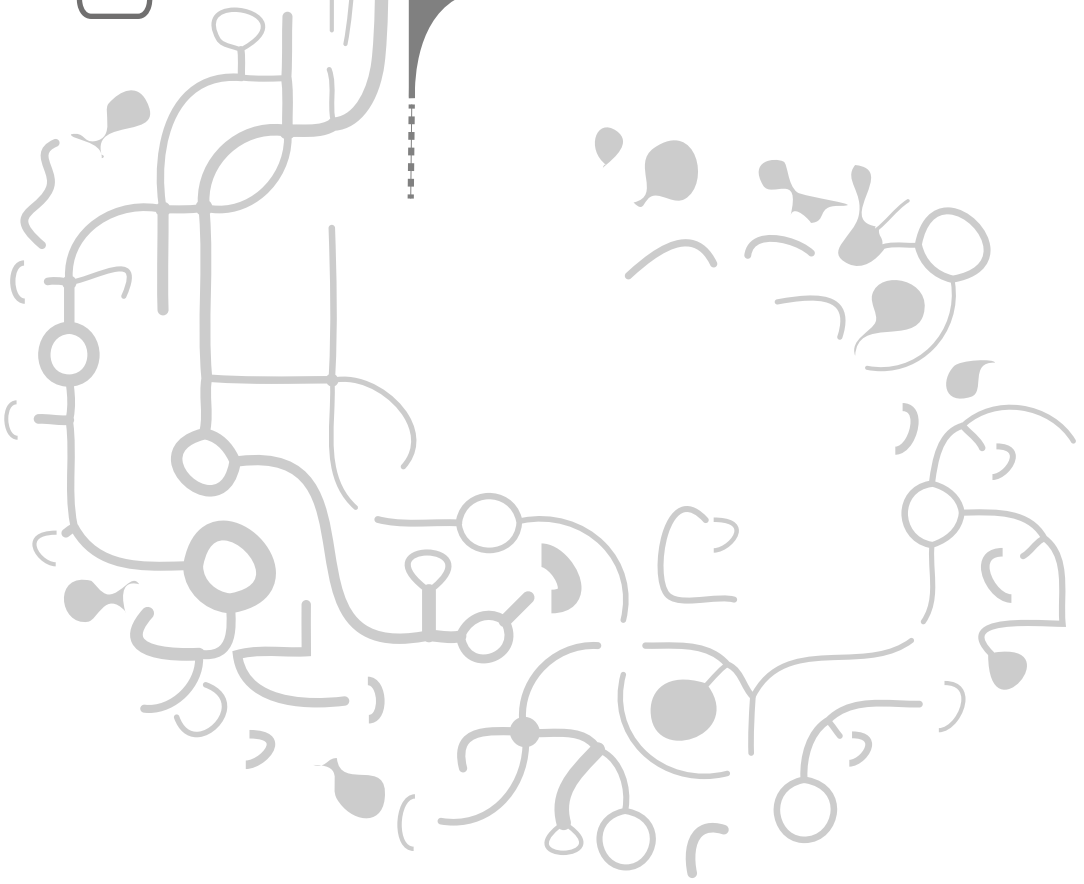
Chapter 6

Summary, General Discussion and Future Perspectives



The overall objective of this thesis was **to better understand cognitive impairment and the underlying neurobiological correlates in MS**. We set out to do so by zooming-in on specific brain structures *a priori* assumed relevant for cognition (thalamus, hippocampus, dorsolateral prefrontal cortex), investigating different levels of cognitive functioning (cognitively preserved, mildly cognitively impaired, cognitively impaired, see Box 1, Chapter 1) and by making use of several imaging modalities (both conventional and advanced measures). We were able to link functional and structural changes in specific areas of the brain to cognitive impairment in MS. The previous chapters described these studies in detail. This chapter will summarize the main findings and will answer the research questions defined in Chapter 1. Moreover, in a final reiteration this chapter will close with two major opportunities for future research on cognitive decline in MS, directly ensuing from the present work.

6.1 THALAMUS

In the introduction of this thesis two research questions were proposed with regard to the thalamus and cognitive impairment in MS:

- Which thalamic imaging measure is most instrumental in explaining cognitive impairment in MS?
- Is it possible to distinguish cognitively preserved from cognitively impaired patients based on thalamic pathology as measured with MRI?

Before answering these questions, I will first briefly sum up the results from the different studies on the thalamus and cognitive decline in MS, described jointly in chapter 2.

Thalamic atrophy, white matter integrity within the thalamus, and cognition

In **chapter 2.1**, we measured diffusion tensor imaging (DTI) parameters (fractional anisotropy (FA), mean diffusivity (MD)) and atrophy in the thalamus, in order to elucidate how subtle white matter integrity changes relate to atrophy and how these measures explain MS cognitive impairment. In line with the literature, our results showed that thalamic atrophy was clearly associated with cognitive impairment.[1-3,] However, in addition to this, we showed that skeletonized MD of the thalamus (i.e. WM bundles within the thalamus) added incremental variance (7-13%) to the prediction of cognitive impairment after accounting for thalamic volume loss (which explained ~30% of the variance). After including WM lesion volume in the regression model, MD survived as predictor only for information processing speed. This indicates that subtle damage to

afferent projections involving the thalamus (i.e. lesions within thalamocortical tracts) may be more responsible for cognitive decline in MS than was previously thought.

Groups of thalamic nuclei and their associated tracts

To follow up on the previous study and the hypothesis we ended with in the previous paragraph, our next work (**chapter 2.2**) focused on the different afferent pathways of the thalamus. The main aim was to investigate different thalamic nuclei (anterior, posterior, medial, lateral) and the integrity of their associated white matter tracts with regard to cognitive impairment and neuropsychiatric symptoms in MS patients. A stereotactic atlas obtained from histopathology data[4] was used to localize the different nuclei and allowed us to study the thalamus and its connected WM tracts with improved anatomical accuracy. DTI parameters and information on lesion volume within the tracts were calculated. In MS patients, FA was moderately correlated with cognitive test scores and disinhibition, *exclusively* when assessing the tract emanating from the anterior part of the thalamus. This indicates that FA changes in the anterior thalamic tract were the most specific marker for cognitive impairment and disinhibition.

Clinical relevance of thalamic pathology

After investigating thalamic changes locally to changes in thalamic pathways, the next important step was to investigate the clinical relevance of these thalamic changes. In **chapter 2.3**, our main aim was to investigate whether changes in functional connectivity, diffusivity and thalamic volume could explain different severities of cognitive impairment in MS (see Box 1, Chapter 1). Thalamic volume loss was seen in all patient groups (cognitively preserved, mild cognitively impaired and cognitively impaired), but was most pronounced in the cognitively impaired patients (20% thalamic volume loss versus 7% in the cognitively preserved and mild cognitively impaired groups). Thalamic DTI metrics showed a similar pattern, with the most severe changes in MD values in the cognitively impaired group. Likewise, increased connectivity of the thalamus with the ventral stream and sensorimotor areas was solely detected in the most severely impaired patients. This shows that MR measures of thalamic pathology allowed us to differentiate between cognitively impaired and cognitively preserved MS patients. Unfortunately, we were unable to identify patients 'at risk' for cognitive decline (i.e. no differences were detected between cognitively preserved and mildly cognitively impaired MS patients).

Discussion

In line with the previous literature, thalamic atrophy showed consistently strong correlations with cognitive performance.[1,5-8] Next, independently from thalamic atrophy, increased MD within the thalamic WM and the associated thalamic tracts was correlated with worse cognitive performance. Changes in thalamic MD have been confirmed in different patient cohorts.[9] This makes both thalamic atrophy and changes in thalamic MD sensitive markers for cognitive impairment. However, thalamic atrophy explains a greater part of the variance of cognition therefore being the strongest predictor for cognition.

While changes in MD are rather sensitive to detect cognitive impairment, changes in FA seem to be more specific in terms of spatial location (i.e. decreased FA exclusively in the anterior tract of the thalamus was correlated to worse cognition). Finally, we found increased connectivity of the thalamus associated with worse cognition. Recently, other studies showed increased thalamocortical functional connectivity associated with cognitive impairment.[10,11] What the increased connectivity of the thalamus with other cortical structures means in terms of cognition, is at present unclear and further research on this topic is needed.

Based on the above, it becomes clear that it is not easy to determine *which thalamic measure is most instrumental in explaining cognitive function* in MS. All thalamic measures showed a correlation with cognitive performance. Therefore, the main challenge now, is to determine the exact order in which thalamic changes (atrophy, diffusion changes, connectivity changes) occur and how this relates to cognitive impairment in MS. Ideally, we would also like to investigate which (histo)pathological mechanisms are reflected in the different thalamic imaging measures.

Yes, cognitively preserved patients could be distinguished from cognitively impaired patients based on thalamic measures. Unfortunately, the thalamic measures were not able to differentiate between cognitively preserved and mild cognitively impaired patients. This suggests that either in terms of pathology these groups are not different, or the currently used measurements were not sensitive enough to detect subtle changes between these two cognitive phenotypes. In my opinion, the second explanation is most reasonable and future studies should explore more sensitive measurements, such as MR spectroscopy and task-specific functional MRI to pursue finding markers associated with the earliest stages of cognitive decline.

6.2 HIPPOCAMPUS

Chapter 3 focuses on cognitive (memory) function in relation to hippocampus pathology as measured with MRI. From previous histopathology studies it was known that extensive demyelination is present in the hippocampus of MS patients.[12-14] *In vivo* MR studies using DIR imaging, showed on average 2-3 hippocampal lesions per patient.[15,16] Moreover, high resolution MR imaging demonstrated atrophy of the hippocampus, especially in the cornu ammonis (CA) 1 region, extending towards the other CA regions in secondary progressive MS patients.[17] These structural hippocampal changes correlated with worse memory performance as measured with neuropsychological tests. A next step was to study the functional characteristics of the hippocampus as measured with MRI, such as functional connectivity and functional activation (i.e. brain activation during a memory task). The following questions posed in the introduction were answered in this thesis:

- How 'well' does the MS hippocampus perform during a memory task in the presence of structural hippocampal damage, and is this performance different for cognitively preserved patients compared to cognitively impaired patients?
- Which hippocampal imaging measure (lesions, atrophy, functional performance) is the best predictor for memory performance in MS?

Hippocampal changes in patients with an intact spatial memory

In **chapter 3.1**, MS patients with an intact spatial memory function were investigated using structural and functional (connectivity) measures. Hippocampal atrophy was already detected in this cognitively preserved stage. Decreased functional connectivity (as measured with resting-state fMRI) between the hippocampus and its target areas (anterior cinglulate cortex, thalamus, prefrontal cortex) was demonstrated in both patients with and without hippocampal atrophy, although more pronounced in the latter group. These structural and functional changes were detected while memory scores on the neuropsychological tests were similar to those of the healthy controls. An important new question arising from this work is whether these brain changes precede overt cognitive impairment and/or whether they reflect a compensatory mechanism to preserve cognitive functioning for as long as possible?

Preserved versus impaired

We continued this line of research by comparing cognitively preserved and cognitively impaired MS patients (see box 1, Chapter 1). Functional brain activation was investigated in response to an episodic memory task inside the scanner. Cognitively preserved and cognitively impaired MS patients did not differ on demographical variables neither on structural MRI measures, including hippocampal volume and number of hippocampal

lesions. The only difference that was detected between these two patient groups, was the increased (cognitively preserved patients) versus decreased (cognitively impaired patients) brain activation ((para)hippocampus, cingulate gyrus) during the correct encoding of images (**Chapter 3.2**; Box 1 Functional Reorganization).

The most informative neuroimaging predictor for memory problems in MS

In **chapter 3.3** the neuroimaging measures obtained in the abovementioned studies were combined to build one comprehensive model including all different hippocampal measures. Hippocampal lesions, hippocampal volume, hippocampal resting-state connectivity and hippocampal activation during a task were all included in a model to identify the best explanatory measure(s) of memory function in MS. This revealed that decreased hippocampal activation and increased hippocampal resting-state connectivity (between the left hippocampus and the right posterior cingulate) were the most important neuroimaging predictors for worse memory performance. Interestingly, hippocampal activation and hippocampal connectivity were not correlated to each other, indicating that both measures explain a different part of the variance in cognitive functioning. Male sex was also a predictor for worse memory performance. This does not come as a surprise, although male patients are less prone to develop MS, they typically show a worse disease course including more cognitive symptoms.[18]

Discussion

How 'well' does the MS hippocampus perform during a memory task in the presence of structural hippocampal damage, and is this performance different for cognitively preserved patients compared to cognitively impaired patients?

Our results showed the presence of structural and functional changes within the hippocampus of patients *with* and *without* cognitive impairment. During an episodic memory task, cognitively preserved MS patients showed increased activation of the hippocampus and associated areas. The opposite was found in cognitively impaired patients: decreased activation of the hippocampus and associated areas. We hypothesize that the different activation patterns reflect different phases in the functional reorganization hypothesis (see Box 1 and Figure 1). Yet, due to the cross-sectional character of these studies, firm conclusions about the chronological order of functional changes and cognitive impairment in MS cannot be drawn. For instance, it is unknown whether cognitively preserved MS patients will eventually develop cognitive impairment and whether cognitively impaired patients already had increased brain activation before entering the cognitive impairment phase. Supporting our hypothesis, a longitudinal associative memory study in healthy elderly without dementia showed that over time clinical decline was accompanied by significant loss of hippocampal

activation.[27] However, to better understand the functional reorganization mechanism in relation to cognitive decline in MS, longitudinal studies are an essential next step.

BOX 1. Functional reorganization

Several previous fMRI studies reported increased functional activation (i.e. increased activation in the same areas that are normally involved in that particular function (enhancement) or activation in other/new brain regions) in MS patients, which related to preserved motor and cognitive function.[19-26] This increased brain activation in the preserved patients possibly reflects a compensatory mechanism, i.e. their brain is working 'harder' to achieve similar results on the neuropsychological examination compared to controls. We hypothesize that cognitively preserved MS patients show functional reorganization to maintain cognitive functioning on a 'normal' level, whereas in cognitively impaired patients this compensatory mechanism is not present anymore, leading to the overt cognitive problems. (see Figure 1)

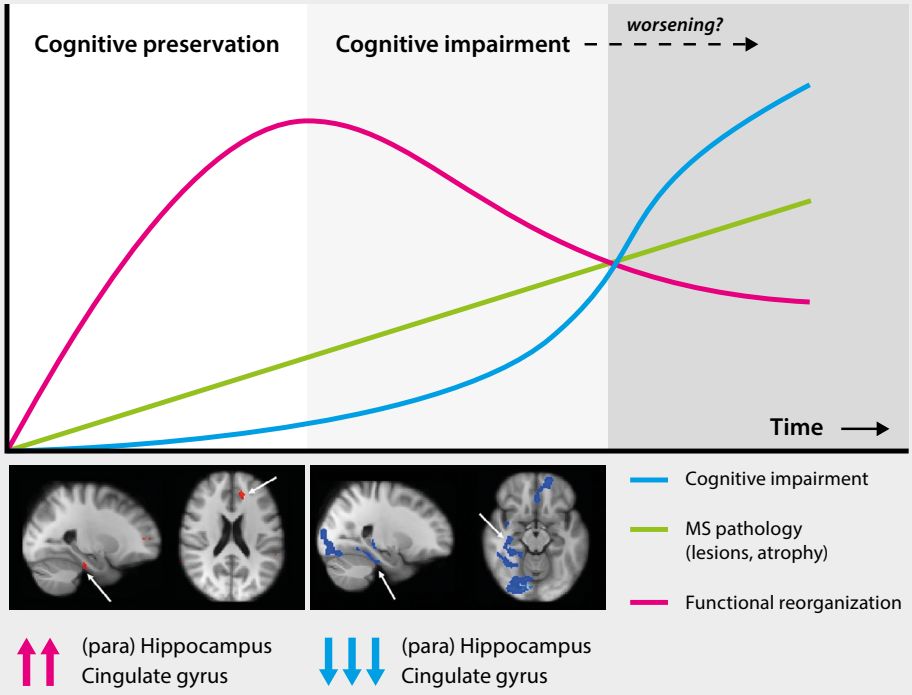


FIGURE 1. Functional reorganization of the hippocampus in MS

a. Cognitively preserved (lightest gray, left box): Cognitively preserved patients show limited structural damage (green line). Functional reorganization is triggered by this incipient damage (pink line). As a result, brain areas normally involved in e.g. a memory task will become more active and additional areas will be recruited (MRI, left: cognitively preserved MS patients, with 'boosted' brain activation).

b. Cognitive impairment (middle and right box): Over time, structural damage increases (green line), but functional reorganization is naturally limited, leading to clinically measurable cognitive decline (MRI, right: cognitively impaired MS patients, reduced brain activity in response to a task).

Moreover, it is of high interest to study the interplay between measures of activation and measures of connectivity. Task-specific fMRI triggers activation in very specific brain regions associated with the task at hand. Increased activation in particular brain structures suggests the presence of a local compensatory process that is successful in preserving one particular cognitive function to a certain degree. This local change in activation does not substantially affect the network dynamics of the 'rest' of the brain. On the contrary, changes in brain connectivity may have effects that are widespread, influencing functions of other connected brain structures. As a result, these connectivity changes might have a disadvantageous influence on cognitive function, i.e. every disbalance that is caused, will negatively influence cognitive performance. It can be hypothesized that local changes in brain activation will eventually trigger global changes influencing the brain's network, leading to cognitive symptoms. However, again, longitudinal studies are necessary to unravel the exact relationship between changes in activation and connectivity.

Based on the above and similarly to the thalamus, there is currently *not one specific hippocampal neuroimaging predictor* for memory impairment in MS. Several hippocampal markers are associated with memory impairment in MS. However, it seems that the functional measures are more sensitive to detect memory impairment compared to the structural hippocampal measures. That is something we should keep in mind when planning new studies.

6.3 DORSOLATERAL PREFRONTAL CORTEX

In chapter 4, the dorsolateral prefrontal cortex (DLPFC) was highlighted in relation to working memory performance, a cognitive deficit that is present in up to 30% of all the MS patients.[28,29] With regard to this brain structure, the following questions are still open:

- Comparing cognitively preserved and cognitively impaired MS patients during a working memory task: what happens to the DLPFC?
- Will activation and functional connectivity of the DLPFC of MS patients be altered after repetitive transcranial magnetic stimulation? If so, how?

Activation of the DLPFC and cognitive impairment

Chapter 4.1 describes the results of a multicenter fMRI study aiming to define the functional correlates of cognitive decline in MS. At six European sites a working memory paradigm, the N-back task, was used to investigate 42 MS patients and 52 healthy controls. Patients were classified as cognitively preserved (47%) and cognitively impaired (53%) and were relatively homogenous in terms of disease type (RRMS), disease severity (EDSS ≤ 4) and disease duration (≤ 15 years).

During the N-back task, healthy controls and MS patients showed activation in several regions located in the fronto-parietal lobes, insula and cerebellum. The activation in these regions increased linearly with task difficulty. A comparison between cognitively preserved and cognitively impaired MS patients demonstrated an association between better cognitive performance and increased activation of the right DLPFC. The increased activation in the preserved patients is assumed to reflect a compensatory mechanism. This is in line with the previous literature on working memory performance in different stages of MS[19,23] and is similar to activation patterns that we found in the hippocampus of MS patients (chapter 3.2).

Repetitive transcranial magnetic stimulation of the right DLPFC

In **chapter 4.2** a first step towards cognitive rehabilitation was taken using repetitive transcranial magnetic stimulation (rTMS). rTMS is a non-invasive technique that can enhance the excitability of a particular cortical region and its connected brain regions.[30,31] Therefore it might be useful for 'regaining' brain function in MS patients with cognitive deficits. In a pilot study, we investigated the effects of a *single* session of high-frequency rTMS (compared to baseline and compared to sham stimulation) on the right DLPFC in MS patients compared to healthy controls. The main outcome parameters were functional activation during an N-back task, functional connectivity changes during the N-back task, and working memory performance (N-back task accuracy).

All 17 patients included in this study were cognitively preserved. Again, increased task-related activation was seen in the left DLPFC and the right temporal pole in patients compared to controls at baseline. This increased task-related activation at baseline in the patient group disappeared after rTMS without influencing the task accuracy. This suggests that the task-related activation became more similar to that of healthy controls after a single session of rTMS. Only in the patient group, increased functional connectivity between the right DLPFC (stimulated area) and task-relevant areas was found after rTMS when compared to sham stimulation. The results of this pilot study suggest a possible beneficial effect of rTMS on working memory in MS patients, but more work needs to be done to further reinforce this conclusion.

Discussion

Both studies showed clear differences in brain activation patterns between MS patients and healthy controls in response to a working memory task. *What happens to the DLPFC for MS patients with and without cognitive decline?* Similarly to the functional reorganization hypothesis in the hippocampus, we hypothesize based on our studies that the DLPFC will first become more active (cognitively preserved MS patients) to compensate for damage in the brain and to retain working memory performance. Then, at a certain moment the DLPFC gets exhausted and becomes less active. This in turn, leads to impaired working memory performance (see Box 1).

Our next question was related to cognitive rehabilitation in MS. *Is it possible to alter the activation and connectivity of the DLPFC in MS patients after rTMS?* Our pilot data demonstrated that this is possible, as the connectivity of the stimulated area with other task relevant areas increased after rTMS compared to sham. Additionally, after rTMS the activation patterns became more like the patterns we see in healthy subjects without negatively influencing working memory performance. This is a first indication that rTMS might be beneficial for boosting the working memory network. An important drawback of this study was that only cognitively preserved patients were included. It would be highly relevant to investigate the effects of rTMS in cognitively impaired MS patients. However, cognitively impaired patients have on average a higher cortical lesion load,[32,33] which is associated with a higher incidence of epilepsy.[34] As epilepsy is a rare but recognized side effect of rTMS, all patients with a high cortical lesion load were excluded from participation. For future cognitive rehabilitation studies, rTMS might not be the best cognitive intervention since safety reasons tend to exclude the patient group that needs therapy most. However, since working memory problems are relatively frequent in MS, '(re)training' the DLPFC still appears to be an interesting target for cognitive rehabilitation.

6.4 UNDERSTANDING COGNITIVE DECLINE

In chapter 2, 3 and 4 we used very specific, hypothesis-driven approaches, concentrating on individual brain regions, relating changes in function and structure to specific cognitive symptoms. In the era of the Human Connectome Project, we know that focusing on one particular brain structure is a simplification of something that is in reality far more complex. Therefore in chapter 5, two descriptive studies were performed looking for differences in the whole-brain.

Whole-brain white matter integrity, lesions and gray matter volume

In **chapter 5.1**, the impact of white matter integrity, white matter lesions and gray matter volume on cognitive performance was investigated without a clear *a priori* hypothesis. Changes in fractional anisotropy were detected in 49% of the investigated white matter in the cognitively preserved patients compared to 76% of the investigated white matter in the cognitively impaired patients. While white matter damage was partly overlapping in both patient groups, the areas that were solely damaged in the impaired patients were highly relevant for cognitive functioning (cortical brain areas, thalamus, brainstem and cerebellum). Interestingly, no differences were found in lesion or atrophy measures between the patient groups, indicating that – of these structural measures – only the white matter integrity separates the cognitively preserved from the cognitively impaired MS patients. This work showed that changes in the brain, related to cognition, are widespread and affect more than just one single brain structure.

Objective cognitive functioning is different from subjective cognitive perception

In **chapter 5.2** we predicted overall cognitive functioning (score based on the neuropsychological evaluation) as well as subjective cognitive functioning (i.e. how do patients perceive their cognitive performance). Possible whole-brain predictors included in the model were gray- and white matter volume and average FA. Specific measures included hippocampal lesions, hippocampal and thalamic volume, and hippocampal activation during a memory-encoding task. Psychological measures (depression, anxiety, fatigue, sleep difficulties) and disease specific measures (duration, type and severity) were also integrated in the model. Worse objective cognitive function was associated with male sex, lower education, and lower gray matter volume. On the other hand, subjective cognitive complaints were associated with fatigue and less hippocampal atrophy. Indeed, objective cognitive functioning was mainly associated with 'hard' measures, suggesting the presence of a neurobiological cause. This work emphasizes the importance of distinguishing subjective complaints from objective

cognitive problems, especially since the first can sometimes be treated (depression, fatigue) while we currently have no treatment available for the objective cognitive symptoms.

Discussion

The brain cannot be regarded as a collection of several individual areas that function on their own. Areas of the brain are related with each other via structural and functional connections (as briefly mentioned in chapter 2.2). Focusing on one particular brain region and one specific cognitive function definitely taught us much about brain mechanisms that explain the presence of cognitive impairment to a certain extent. However, the time has come to broaden our 'basic' model of the brain by including network measurements in our explanatory model. Recent studies using functional network parameters showed that decreased network efficiency and decreased centrality was related to cognitive impairment in MS.[35] Since cognitively preserved and cognitively impaired patients could be distinguished based on white matter structural integrity, understanding structural (dis)connectivity is especially interesting for further research.

6.5 CONCLUSIONS – WHAT HAVE WE LEARNED FROM THIS THESIS

Thalamus

- In addition to thalamic volume, changes in mean diffusivity (MD) within the thalamus add 7-13% to the explained variance in predicting cognitive impairment;
- Fractional anisotropy (FA) changes in the anterior thalamic tract were the most specific marker for cognitive impairment and disinhibition;
- Based on thalamic pathology (i.e. atrophy, changes in MD, connectivity) cognitively preserved patients can be distinguished from cognitively impaired patients

Hippocampus

- Hippocampal atrophy and changes in hippocampal connectivity were already present in cognitively intact MS patients;
- Increased hippocampal activation was associated with cognitive preservation; decreased hippocampal activation with cognitive impairment;
- Functional hippocampal measures are more informative in predicting memory function in MS than structural hippocampal measures

Dorsolateral prefrontal cortex

- Cognitively preserved patients show increased activation during a working memory task;
- A single session rTMS alters brain activation and connectivity in patients with MS;
- Due to safety reasons, rTMS might not be the 1st choice for cognitive rehabilitation in MS

Understanding cognitive decline in MS

- WM integrity changes are most informative in distinguishing cognitively preserved from cognitively impaired MS patients;
- Neuropsychological test scores in MS patients are best predicted by GM volume, male sex and educational level; subjective cognition is mainly a reflection of fatigue;
- Increased activation of brain structures and/or changes in functional connectivity might be seen as 'functional reorganization'; this may be used for cognitive rehabilitation studies

FUTURE PERSPECTIVES

'One day… ***…we will be able to 'treat' cognitive impairment in MS'***

Cognitive rehabilitation in MS: we are certainly not there *yet*. Cognitive impairment in MS is nowadays recognized as one of the most disabling symptoms of the disease. Several studies, including the ones presented in this thesis, showed functional (activation, connectivity) and structural (atrophy, lesions) changes in specific brain regions (i.e. thalamus, hippocampus, DLPFC) that were strongly associated with cognitive impairment. Additionally, using advanced neuroimaging measures, cognitively preserved patients could be distinguished from cognitively impaired patients. Although the understanding of cognitive impairment in MS has advanced substantially, at least two major challenges need to be addressed so that we can move from the current situation towards actual cognitive rehabilitation.

Challenge 1: Further understanding of cognitive decline in MS

Understanding the temporal dynamics of cognitive decline in MS can serve as a guide for (future) cognitive rehabilitation studies. To obtain information on the time course of cognitive impairment in MS, longitudinal follow-up information is required. So far, longitudinal studies on cognitive dysfunction in MS are scarce, and the ones that have been performed followed patients early in the disease course, mostly using conventional MR measures.[36-39] These studies showed that, contrary to cognitive decline in Alzheimer's disease, cognition in MS deteriorates slowly. Approximately 60-100% of the patients still have a stable cognition after two years of follow-up.[36,37,40]

Essential information with regard to the optimal time point to start cognitive rehabilitation lies within understanding the '**tipping point'** ((i.e. the moment when cognitively preserved patients become cognitively impaired, see Figure 2)). What are the main predictors for conversion from cognitive preservation to cognitive impairment? How is this conversion related to changes in brain activation, brain connectivity, and structural brain changes? In our own research group we are starting two longitudinal studies to find answers to these questions. One study will follow a large cohort of early MS patients (already extensively investigated six years after diagnosis), now approximately 10 years after the diagnosis; a second study will follow cognitively preserved and cognitively impaired MS patients (independent of disease type, duration, and severity) approximately five years after the first measurement.

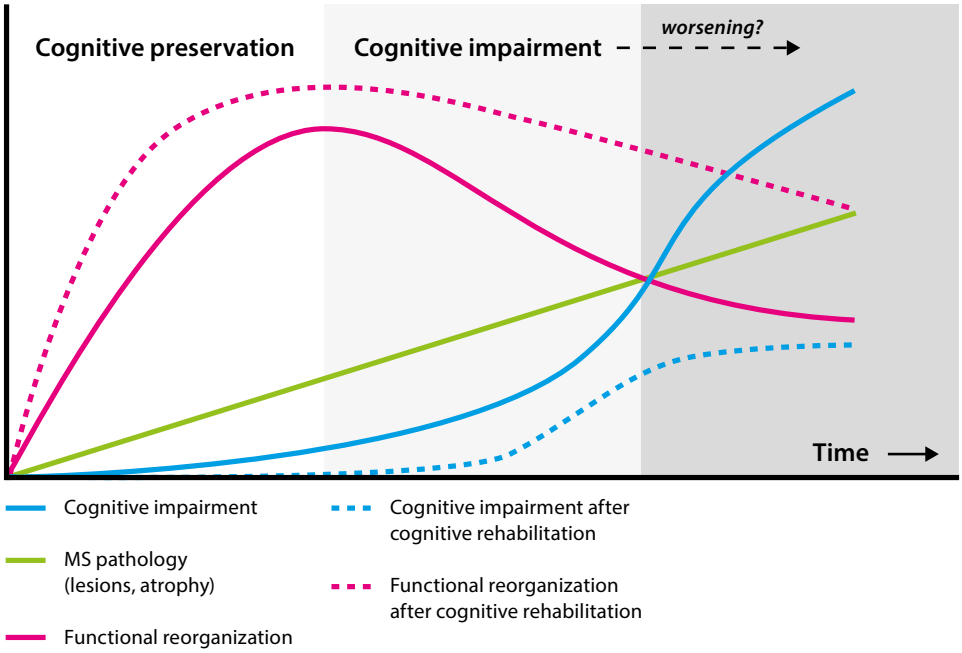


FIGURE 2. The anticipated effects of cognitive rehabilitation

a. Cognitively preserved (lightest gray, left box): Cognitively preserved patients show limited structural damage (green line). Functional reorganization is triggered by this incipient damage (pink line).

b. Cognitive impairment (middle and right box): Over time, structural damage increases (green line), but functional reorganization is naturally limited, leading to clinically measurable cognitive decline.

c. Expected effect of cognitive rehabilitation: The effects of cognitive training should lead to prolonged functional reorganization (dotted pink line; in the cognitively preserved patients this means preventative; in the cognitively impaired patients this means improved cognitive function), compensating (partly) for cognitive impairment (dotted blue line).

Challenge 2: Start rehabilitation

While we need to expand our understanding of the temporal dynamics of cognitive decline in MS, we should simultaneously start exploring potential candidates for cognitive rehabilitation. The key question will be whether it is possible to influence cognitive performance beneficially via several rehabilitation strategies such as cognitive training, pharmacological intervention, and transcranial magnetic stimulation (TMS; already explored in Chapter 4.2). The main goal will be to improve cognitive functioning (i.e. cognitively impaired MS patients) or to prevent cognitive impairment to occur (i.e. cognitively preserved MS patients), see Figure 2.

Until now, cognitive rehabilitation studies in MS are limited and largely report

contradicting results.[41-49] The inconsistency of the results is most likely due to methodological issues, such as relatively small sample sizes, inadequately defined groups (i.e. too liberal criteria for cognitive impairment) and incorrect matching. This conclusion was confirmed by a clinical trial by one of the leading groups in the field,[43] which showed that improved learning and memory performance as a result of a memory-training program was uniquely found in moderately cognitively impaired patients. The mildly impaired individuals did not show any effect from the training. Future studies need to pay careful attention to these methodological problems. There are a few approaches that are potentially of interest:

- *Cognitive training - Concentration*

One of the cognitive domains that is highly attractive for cognitive rehabilitation in MS is attention. Deficits in attention are frequently found in MS patients, and pilot data on cognitive rehabilitation programs focusing on attention and concentration in MS showed promising results.[45,46] We recently received financial support from the Dutch MS Research foundation to investigate the effects of a **7-week attention training.** We plan to study MS patients with (n=30) and without (n=30) attention problems, using the cognitive rehabilitation program C-Car (Concentration Car).[50,51] C-Car is an already an established training program; it includes several aspects of attention: sustained attention, divided attention, focused attention, and alternative attention. The effects of C-Car will be monitored with structural and functional MR imaging, neuropsychological testing and questionnaires on subjective cognitive functioning to investigate the effectiveness of the training on these three different outcome levels (brain mechanisms, objective and subjective cognitive functioning).

- *Cognitive training - Memory*

Hippocampal changes (i.e. atrophy, lesions) and memory problems are very often found in MS patients.[14,52,53] Therefore, an intervention influencing hippocampal-memory function would be one of the first choices for cognitive rehabilitation. Unfortunately, such a training program is currently not available.

Previous studies have shown that it is possible to train the hippocampus and improve memory function.[54,55] For example, exercise enhances learning, improves memory retention and is accompanied by an increased cell proliferation and survival in the hippocampus of rodents.[56,57] In humans, physically fit elderly have larger hippocampal and medial temporal lobe volumes; larger hippocampal volumes mediate improvements in spatial memory.[58]

Based on these principles, it would be very promising to develop a **hippocampal-memory-rehabilitation program**. We are currently (in collaboration with Prof. Sitskoorn/ Dr. Gehring, Tilburg University and with support of the Neuroscience Campus Amsterdam) exploring the possibilities for such an intervention program. The ultimate goal is to combine physical exercise (home trainer, personalized cycling activity) with a computerized hippocampal-memory training (concurrently). In the future this hopefully gives opportunities to improve memory function in MS patients.

- *Pharmacological intervention – Memory*

Cognitive training programs are quite demanding for patients in terms of frequency and duration, which makes it worthwhile to additionally explore **pharmacological treatment** for cognitive impairment. Based on the literature, one of the most promising options is to manipulate the cholinergic system using acetylcholinesterase inhibitors. Several studies investigated this type of intervention, showing inconsistent effects on memory function.[59-63] However, it might be that a higher-dosage of the drug is necessary to exert a beneficial effect on cognition in MS specifically. A post-mortem study from our own group demonstrated decreased activity of the enzyme choline acetyltransferase (ChAT) in the hippocampus, while the activity of the degrading enzyme, acetylcholinesterase (AChE) was unaltered.[64] This cholinergic imbalance was not seen in the hippocampus of Alzheimer's patients where both ChAT and AChE were decreased. In MS, a stronger inhibition of AChE, as realized by a higher dose of donepezil, might be appropriate to rebalance cholinergic neurotransmission and improve cognitive functioning in MS.[64,65] Therefore, a dose-response study would be a step forward and should carefully weigh the advantages against the possible side effects.

Besides the cholinergic system, investigating the effects of standard disease modifying drugs and the newer medications such as natalizumab and fingolimod on cognitive impairment in MS will be highly relevant.


TO-DO-LIST
1) Further UNDERSTANDING
- Start longitudinal studies on cognitive impairment in MS
- Find predictors for the 'tipping point' (i.e. the moment when cognitively preserved patients become cognitively impaired) and investigate the relationship with changes on MRI
2) Start REHABILITATION
- Start cognitive rehabilitation studies in MS patients
- Develop new cognitive training programs
- Explore possibilities for pharmacological intervention